(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 189 306**
A2

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: **86300382.8**

(22) Date of filing: **20.01.86**

(51) Int. Cl.⁴: **C 07 H 23/00**, A 61 K 31/70

(30) Priority: **22.01.85 US 693416**
27.09.85 US 781438

(43) Date of publication of application: **30.07.86**
Bulletin 86/31

(84) Designated Contracting States: **AT BE CH DE FR GB IT LI LU NL SE**

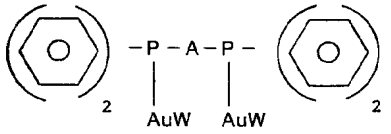
(71) Applicant: **SMITHKLINE BECKMAN CORPORATION, One Franklin plaza, Philadelphia Pennsylvania 19103 (US)**

(72) Inventor: **Hill, David Taylor, 109 Magnolia Place, North Wales Pennsylvania 19154 (US)**
Inventor: **Johnson, Randall Keith, 71 Lianfair Circle, Ardmore, PA 19002 (US)**

(74) Representative: **Waters, David Martin, Dr. et al, Smith Kline & French Laboratories Ltd. Patent Department Mundells, Welwyn Garden City Hertfordshire AL7 1EY (GB)**

(54) **[alpha,W-bis(diphenylphosphino)hydrocarbon]bis[(thiosugar)-gold]and bis[selenosugar)gold]derivatives.**

(57) Compounds of formula (I)



(I)

wherein A is $(CH_2)_n$ or cis CH = CH; n is 1 to 6; and W is the same and is thiosugar or selenosugar, processes for their preparation, pharmaceutical compositions containing them and their use in therapy as inhibitors of tumor cell growth.

EP 0 189 306 A2

TITLE

[α,ω-BIS(DIPHENYLPHOSPHINO)HYDROCARBON]BIS[(THIOSUGAR)GOLD] AND BIS[SELENOSUGAR)GOLD] DERIVATIVES

BACKGROUND OF THE INVENTION

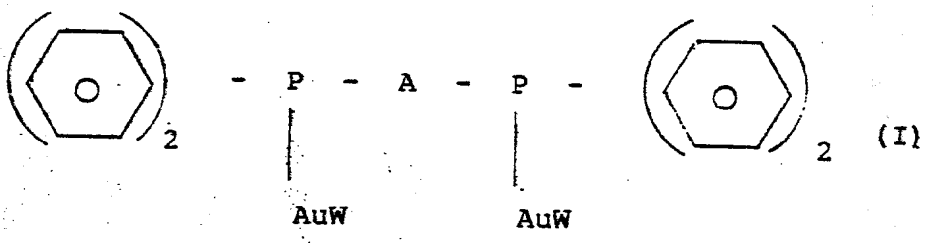
This invention relates to novel [bis(diphenylphosphino)alkyl]bis-gold[I] derivatives which have tumor cell growth-inhibiting activity, pharmaceutical compositions containing such novel derivatives, and a method for treating tumor cells sensitive to such derivatives by administering tumor cell growth-inhibiting amounts of such novel derivatives to a host animal afflicted by such tumor cells.

Sutton et al., J. Med. Chem., 15 (11), 1095-98 (1972), disclose antiarthritic properties of certain trialkylmonophosphine gold thiosugar complexes. Mirabelli et al., Proc. Amer. Assn. Cancer Res., 25, 367 (1984) disclose that certain monophosphinegold (I) thiosugar complexes, including auranofin and related triethylphosphino gold(I) thiolates, had respectable activity in an intraperitoneal P388 leukemia tumor model. Simon et al., Cancer Res., 41, 94 (1981), and Mirabelli et al., Cancer Res., 45, 32 (1985),disclose that auranofin possesses significant antitumor effects in animals bearing P388 leukemia. Dumas et al., Japanese Patent Application 58,192,893, published November 10, 1983, disclose the

selenium analog of auranofin and other related triethylphosphino gold(I) selenolates, and report their utility as antiarthritic agents. Struck et al., J. Med. Chem., 9, 414-16 (1966), disclose cytotoxic activity of ethylenebis(diphenylphosphine). None of the aforementioned references disclose or suggest the [bis(diphenylphosphino)alkyl]bis-gold(I) thiosugar or selenosugar derivatives of the instant invention, or that they have tumor cell growth-inhibiting activity.

SUMMARY OF THE INVENTION

This invention relates to diphenylphosphino gold [I] derivatives of the formula:



(I)

wherein:

A is $(CH_2)n$ or cis CH=CH;

n is 1 to 6; and

W is the same and is thiosugar or selenosugar.

The attachment of W to the gold atom is through the sulfur atom of the thiosugar or selenium atom of the selenosugar.

This invention also relates to a pharmaceutical composition which comprises an effective, tumor cell growth-inhibiting amount of an active ingredient and an inert, pharmaceutically acceptable carrier or diluent, wherein said composition is useful for inhibiting the growth of animal tumor cells sensitive to the active ingredient, and wherein the active ingredient is a compound of formula (I).

Another aspect of this invention is a method of inhibiting the growth of animal tumor cells sensitive to a compound of formula (I) which comprises administering to an animal afflicted with said tumor cells, an effective, tumor cell growth-inhibiting amount of a compound of formula (I).

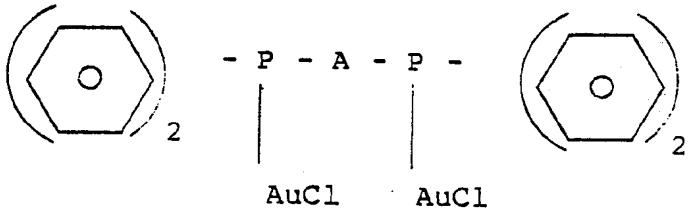
DETAILED DESCRIPTION OF THE INVENTION

By the term "thiosugar" is meant any 1-thioaldose. Examples of such thiosugars include 1-thioglucose, 1-thiogalactose, 1-thiomannose, 1-thioribose, 1-thiomaltose, 1-thiofucose, tetra-O-acetyl-1-thioglucose, tetra-O-acetyl-1-thiomannose, tetra-O-acetyl-1-thiogalactose, tri-O-acetyl-1-thioribose, hepta-O-acetyl-1-thiomaltose, tri-O-acetyl-1-thiofucose.

By the term "selenosugar" is meant any non-acetylated 1-selenoaldose. Examples of such selenosugars include 1-selenoglucose, 1-selenomannose, 1-selenogalactose, 1-selenoribose, 1-selenomaltose and 1-selenofucose.

Preferred compounds of formula (I) include those wherein W is 1-thioglucose, 1-thiogalactose and 1-thiomannose. These compounds are preferred because they exhibit particularly active tumor-inhibiting activity in a variety of test systems.

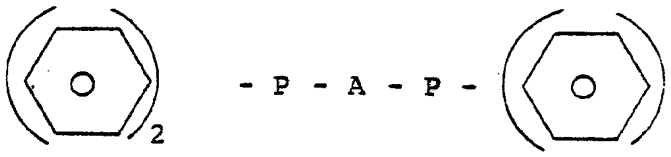
All the compounds encompassed by formula (I) can be prepared by methods available to one skilled in the art. Generally, the compounds of formula (I), wherein W is a non-acetylated 1-thioaldose or 1-selenoaldose, are prepared by reacting the appropriate derivative of formula (II):



(II)

wherein A is as defined above, with the appropriate sodium thiosugar or sodium selenothiosugar. The desired non-acetylated thiosugar or selenosugar can be obtained commercially or by methods available to one skilled in the art.

The desired derivative of formula (II) can be obtained by reacting the appropriate diphosphino hydrocarbon of formula (III):



(III)

wherein A is as defined above, directly with chloroauric acid hydrate or a reduced form of the acid hydrate obtained by treatment with thiodiglycol. For example, a solution of thiodiglycol in a nonreactive organic solvent, such as methanol or ethanol, is reacted with an aqueous solution of chloroauric acid hydrate cooled to a temperature of from -10 to 0°C, and then treated with a solution of the appropriate formula (III) compound in a nonreactive organic solvent system, such as a mixture of chloroform and methanol, for from one to two hours to give the corresponding formula (II) compound. Similarly, chloroauric acid hydrate in a nonreactive organic solvent, such as methanol or ethanol, is reacted with a solution of the appropriate formula (III) compound at ambient temperature for from one to two hours to give the corresponding formula (II) compound. All formula (III) compounds necessary as starting materials for making the formula (II) compounds are available commercially, for example, from Strem Chemicals Inc., Danvers, Massachusetts.

The compounds of formula (I) wherein W is a per-O-acetyl thiosugar can be prepared by reacting the

appropriate derivative of formula (II) with the appropriate per-O-acetyl- (thiopseudourea hydrobromide), all of which are available commercially or can be prepared by methods available to one skilled in the art. See, for example, Durette et al., Carb. Res., 81, 261 (1980).

As an alternate route, the compounds of formula (I) wherein W is a non-acetylated thiosugar or selenosugar can be prepared from the corresponding per-O-acetyl derivative by treating the acetylated compound with a hydrolyzing base, such as methanolic ammonia or sodium methoxide in methanol, to give the desired non-acetylated compound of formula (I). The appropriate per-O-acetyl selenosugar starting material can be prepared by reacting the appropriate derivative of formula (II) with the appropriate per-O-acetyl-(selenopseudourea hydrobromide), all of which are available commercially or can be prepared by methods available to one skilled in the art. See, for example, Durette et al., Carb. Res., 81, 261 (1980.

As stated above, the compounds of formula (I) have tumor cell growth-inhibiting activity which has been demonstrated in a variety of test systems.

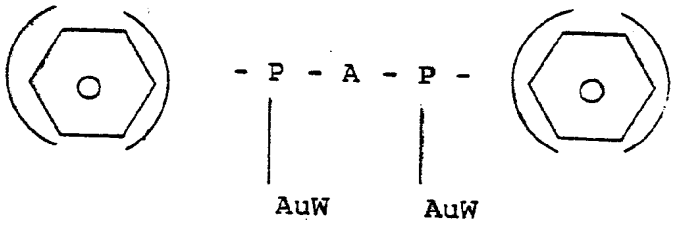
The B16 mouse melanoma cell assay measures the ability of a compound to inhibit the clonogenic capacity of cells in vitro following a two hour exposure to the compound. The cytotoxic activity of the compounds of formula (I) was evaluated in vitro using B16 melanoma cells according to the following protocol:

B16 melanoma (highly metastatic subline, F10) are used and maintained as monolayer cultures in Minimal Essential Media (Grand Island Biological Co., Grand Island, N.Y.) supplemented with 10% calf serum, 1% antibiotics in a 5% CO_2 humidified incubator at 37°C. Asynchronous populations of cells are harvested and replated to 5000 cells/plate in sterile 60 mm x 15 mm

petri plates. Plates are incubated overnight to allow attachment of the cells to the plate. Cells are treated with the compound to be evaluated under sterile conditions, allowed to react for 2 hours followed by aspiration of medium. Plates are washed one time with 5 ml of phosphate buffered saline (PBS), followed by the addition of 5 ml of fresh media. Plates are incubated for 5 days at 37° in a CO_2 incubator. Viability is measured by the ability of a cell to form a colony of greater than 50 cells. Colonies are fixed with 0.5% crystal violet in 95% ethanol. Plates are dried and counted with a Biotran III Automatic Count Totalized (New Brunswick Scientific Co., Edison, N.J.). Mean and standard deviation of triplicate samples are determined for each drug concentration. The data are analyzed by plotting the log of the survival fraction (number of colonies in drug treated plates/number of colonies in controls) versus the drug concentration.

An evaluation of one particular compound of formula (I) in the <u>in vitro</u> B16 cytotoxic assay is shown in Table I.

TABLE I



Compound No.	A	W	IC_{50} (+FCS) (a) (μM)
1	(CH_2)	1-thioglucose	1 ± 0.2

(a) concentration of drug which inhibits cloning efficiency of B16 melanoma cells by 50% upon 2-hour exposure; drug exposure in the presence of 10% fetal calf serum.

Additionally, in another in vitro assay, Compound No. 1 effectively killed HT-29 human colon carcinoma cells, with an IC_{50} (+FCS) of 5 μM following a 2 hour exposure.

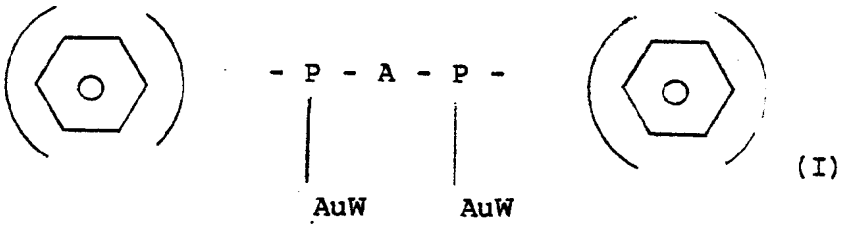
P388 lymphocytic leukemia is currently the most widely used animal tumor model for screening for antitumor agents and for detailed evaluation of active compounds. This tumor system is widely accepted as an antitumor agent screening tool because it is sensitive to virtually all of the clinically active antineoplastic agents; quantitative and reproducible; amenable for large-scale screening; and predictive for activity in other animal tumor models. Drugs that are highly active in intraperitoneal (ip) P388 leukemia are generally active in other tumor models as well. The antitumor activity of the compounds of formula (I) is demonstrated in the P388 leukemia mouse model employing the following protocol:

10^6 P388 leukemia cells are inoculated ip in $B6D2F_1$ mice. Twenty-four hours later, if the tumor inoculum proves to be free of bacterial contamination (as determined by 24 hours incubation in thioglycollate broth), animals are randomized into groups of 6 and housed in shoebox cages. The compound to be evaluated is dissolved in a minimal volume of either N,N-dimethyl-acetamide (DMA) or 95% ethanol (depending upon solubility). An equal volume of saline is added; if the drug comes out of solution an equal volume

of polyethoxylated castor oil is added and then saline qs to a concentration such that the desired dose is delivered in 0.5 ml. The final concentration of DMA, ethanol and polyethoxylated castor oil is 10 percent. Dilutions for lower doses are made with saline so there is a decreasing proportion of organic solvents in the vehicle with decreasing dosage. These vehicles provide soluble formulations (or suspensions). Formulations are prepared immediately prior to injection. The compound is administered ip on Days 1 through 5 (i.e. treatment is initiated 24 hrs after tumor inoculation). Each experiment includes three groups of 6 animals as untreated controls and animals treated with a positive control, cisplatin, at two dose levels. Animals are weighed as a group on Days 1, 5 and 9 and average weight change (Δ wt.) is used as a reflection of toxicity. Each experiment also includes an inoculum titration -- groups of 8 mice inoculated ip with 10^5 to 10^0 P388 leukemia cells. The titration is used to calculate cell kill achieved by treatment with drugs. Animals are monitored daily for mortality and experiments are terminated after 45 days. The endpoint is median survival time (MST) and increase in lifespan (ILS) which is the percentage of increase in MST relative to untreated controls. Untreated controls inoculated ip with 10^6 P388 leukemia cells generally survive for a median of 10 or 11 days. A drug is considered active if it produces $\geq$ 25 percent ILS.

A summary of the evaluation of several compounds of formula (I) in the <u>in vivo</u> P388 model is shown in the following Table A.

TABLE A



(I)

Compound Number	A	W	MTD (a) (μM/kg)	ILS (Max) (b) (%)
1	$(CH_2)_2$	1-thioglucose	5	86 ± 8 (d)
2	$(CH_2)_2$	1-thioglucose (OAC)$_4$ (c)	2.6	35/35/28/95
3	$(CH_2)_2$	1-thiomannose-(OAC)$_4$	2.6	30/30/25
4	$(CH_2)_2$	1-thiogalactose	3.4	85/100/147
5	$(CH_2)_2$	1-thiomannose	5	90/74
6	$(CH_2)_3$	1-thioglucose	5	28/56/41
7	$(CH_2)_2$	1-selenoglucose	9.4	36/27
8	$(CH_2)_2$	1-thioribofuranose	6	50/56

(a) maximally tolerated dose for B6D2F female mice on an ip qDx5 regimen.

(b) maximum increase in lifespan produced in mice bearing ip P388 leukemia (figures separated by slashes indicate data generated in separate experiments).

(c) 1-thioglucose-(OAC)$_4$ = tetra-O-acetyl-1-thioglucose.

(d) number based on data from twelve separate experiments.

Based on the data set forth in Table A, compounds of formula (I) showed significant antitumor activity in the in vivo ip P388 leukemia tumor assay. In particular, Compounds No. 1, 2 and 3 have particularly good activity in the P388 leukemia assay with an ILS comparable to the clinically useful antitumor agent cisplatin.

Another chemosensitive tumor model is intraperitoneally (ip) implanted M5076 reticulum cell sarcoma in mice. In this system B6D2F female mice are inoculated with 0.5 ml of a 10 percent (w:v) brei of M5076 prepared from pooled subcutaneous (sc) tumors excised at about 21 days from C57Bl/6 donors. Drugs are administered ip. Daily treatement is begun 24 hours after implantation and is continued for ten days. The treatment regimen for M5076 is more prolonged than for P388 because of the slower growth rate and longer control survival time of the M5076 tumor. The antitumor activity of Compounds No. 1 and No. 2 of Table A in the M5076 reticulum cell sarcoma tumor model is set forth in Table 2.

TABLE 2

Compound No.(a)	ILS (MAX) (%)(b)	MTD (μM/kg)(c)
1	109/38/45/65	3.4
2	67	2
4	37	3.5
6	35	3.5
7	46	3.1

(a) see Table A for structures.

(b) maximum increase in lifespan produced in mice bearing ip M5076 reticulum cell sarcoma (figures separated by slashes were generated in separate experiments).

(c) maximally tolerated dose for B6D2F female mice on an ip qDx10 regimen.

The cytotoxic activity of Compound No. 1 from Table A was evaluated in vivo using B16 melanoma cells. In this system, groups of eight $B6D2F_1$ mice are

inoculated ip with 0.5 ml of a 10% (w:v) brei of B16 melanoma prepared from pooled sc tumors excised at 14-21 days from $C67B_1/6$ donor mice. Daily treatment is begun 24 hours after tumor implantation and is continued daily for ten (10) days. The route of drug administration is ip. The mice are monitored daily for survival for sixty (60) days. Antitumor activity is assessed by prolongation of median survival time. An ILS of $\geq$ 25% indicates activity in this tumor model.

A summary of the results of the in vivo ip B16 melanoma assay is shown in Table 3.

TABLE 3

Compound No.(a)	MTD (μM/kg)(b)	ILS (%)(c)
1	3.4	37/26

(a) see Table A for structure.

(b) maximally tolerated dose for $B6D2F_1$ mice on an ip of qDx10 regimen.

(c) maximum increase in lifespan produced in mice bearing ip B16 melanoma (figures separated by a slash were generated in separate experiments).

Similarly, in another additional in vivo tumor model, namely B16 melanoma in mice, Compound No. 1 from Table A, administered ip in a dosage schedule of 8, 4, 2, 1 and 0.5 mg/kg produced an average increase in lifespan (ILS) of 32% at a maximally tolerated dose (MTD) of 3.4 μM/kg.

Compound No. 1 from Table A was also tested in a further in vivo tumor model, mammary adenocarcinoma 16/c, a tumor model sensitive to DNA binders and alkylating agents. In this experiment, the tumor was implanted sc in

C3H mice, and the drug was administered ip or iv on an intermittant treatment schedule, i.e., once on days 1, 5, 9, 13 and 17. Tumors were measured 3 weeks after implantation, and activity was assessed by degree of tumor growth inhibition. Cisplatin, a drug which generally produces complete inhibition of the growth of mammary adenocarcinoma 16/c, was used as a positive control. A tumor growth inhibition of $\geq$ 75% indicates that a drug is active in this type of animal tumor model. The results of this assay are summarized in Table B.

TABLE B

Drug	Regimen: Route and Schedule of Administration	Optimal Dose (mg/kg)	Mean Tumor Volume (mm^3) on Day 21	Inhibition (%)	N.P.*
		Experiment 1			
Control			1187 ± 999		1/24
Cisplatin	ip, q4D x 5	6	30 ± 64	97	6/8
Compound No. 1	ip, q4D x 5	12	42 ± 60	96	3/5
		Experiment 2			
Control			1113 ± 626		0/23
Cisplatin	ip, q4D x 5	6	0	100	8/8
	iv, q4D x 5	6	21 ± 61	98	7/8
Compound No. 1	ip, q4D x 5	8	711 ± 268	36	0/7
	iv, q4D x 5	16	243 ± 106	78	0/8

*N.P. = Proportion of mice without palable tumors on Day 21

Likewise, Compound No. 1 from Table A was tested in an additional in vivo tumor model known as ADJ-PC6 Plasmacytoma. In this assay, tumor cells are carried by serial sc passage in BALB/c female mice and then collected aseptically on ca. day 21 and minced in Hank's balanced salt solution. The cells are then dispersed by homogenization in a loose-fitting teflon glass homogenizer, and cell concentration is adjusted to 4×10^6 viable (trypsin blue-excluding) cells per ml by hemocytometer counts. A total of 0.5 ml (2×10^6 cells) is implanted sc on the right flank of BALB/c female mice in groups of 8. Treatment is given ip on Days 1 - 10, and tumors are measured in perpendicular diameters with a vernier caliper on Day 18. Tumor volume is calculated by multiplying length x width^2 x 0.5. Generally, $\geq$ 75% inhibition of tumor growth reflects significant antitumor effect. Cisplatin, the positive control compound, produces complete tumor growth inhibition. The results of this assay are summarized in Table C.

TABLE C

Drug	Dose (mg/kg/dayx10, ip)	Tumor Growth Inhibition (Day 18) N.P.(a)	MTV(b)	% Inhibition
Compound No. 1	6	6/7	11 ± 28	98(c)
Compound No. 1	3	0/8	295 ± 163	50

(a) N.P. = Proportion of mice without palpable tumor on Day 18.

(b) MTV = Mean Tumor Volume (mm^3) on Day 18.

(c) In another experiment at the same dose and same treatment schedule, Compound No. 1 gave only 23% inhibition of ADJ-PC6 Plasmacytoma.

The pharmaceutical compositions of this invention comprise an effective tumor cell growth-inhibiting amount of a compound of formula I and an inert pharmaceutically acceptable carrier or diluent. These compositions are prepared in dosage unit form appropriate for parenteral administration.

Compositions according to the invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions or emulsions. The composition may be in the form of a solution of the active ingredient in a minimal volume of dimethylacetamide or ethanol, for example 5% v/v, brought up to volume with peanut oil or normal saline solution. Polyethoxylated castor oil, for example 2 to 5% v/v, may also be used to solubilize the active ingredient. In addition, the composition may be in the form of a slurry with, for example, hyroxypropyl cellulose or other suitable suspending agent. As an emulsifying agent, lecithin for example may be used. The composition may also be provided in the form of a sterile solid which can be dissolved in a sterile injectable medium immediately before use.

It will be appreciated that the actual preferred dosages of the compounds of formula I used in the compositions of this invention will vary according to the particular compound being used, the particular composition formulated, the mode of administration and the particular site, host and disease being treated. The route of internal administration should be selected to ensure that an effective tumor cell growth-inhibiting amount of the compound of formula (I) contacts the tumor. Optimal dosages for a given set of conditions can be ascertained by those skilled in the art using conventional dosage determination tests in view of the above experimental data. For parenteral administration the dose generally employed is from about 5 to about 20 mg/m^2 of body

surface per day for one to five days, repeated about every fourth week for four courses of treatment.

The method for inhibiting the growth of animal tumor cells sensitive to a compound of formula (I) in accordance with this invention comprises administering to a host animal afflicted with said tumor cells, an effective tumor cell growth-inhibiting amount of a compound of formula I. As described above, during the course of treatment the active ingredient will be administered parenterally in an amount selected from about 300 mg to about 1000 mg.

EXAMPLES

The following examples illustrate the chemical preparation of several compounds of formula I which are used in the compositions and methods of this invention and as such are not to be construed as limiting the scope thereof. All temperatures are in degrees Centigrade.

EXAMPLE 1

μ-[1,2-BIS(DIPHENYLPHOSPHINO)ETHANE]BIS[1-THIO-β-D-GLUCOPYRANOSATO-S)GOLD(I)]

a. μ-[1,2-Bis(diphenylphosphino)ethane]bis-[chlorogold(I)]

Thiodiglycol (11.0g, 0.09 mol) in methanol (50 ml) was added dropwise over 15 minutes to a solution of chloroauric acid tetrahydrate (12.4 g, 0.03 mol) in water (100 ml)/methanol (150 ml) kept at 0°. After stirring an additional 15 minutes, 1,2-bis(diphenylphosphino)ethane (6.12 g, 0.015 mol), obtained from Strem Chemicals, Inc., Danvers, Massachusetts, in chloroform (100 ml)/methanol (100 ml) was added to the colorless solution (immediate ppt upon addition). After warming to room temperature (2 hours), methanol (0.5 l) was added and the product collected, slurried with methylene chloride/ethanol,

filtered and dried to give 11.0 g (85%) of white product which had a melting point of 290-292 °.

By using substantially the method described above and employing the appropriate ligand of formula (III), any other desired derivative of formula (II) can be obtained.

b. μ-[1,2-Bis(diphenylphosphino)ethane]bis[1-thio-β-D-glucopyranosato-S)gold(I)]

Under an argon atmosphere at ambient temperature, μ-[1,2-bis(diphenylphosphino)ethane]bis[chlorogold(I)] (5.0 g, 5.8 mmol), prepared as described in part A, in chloroform (500 ml)/ethanol (200 ml) was added to a rapidly stirred solution of sodium thioglucose (2.53 g, 11.6 mmol), obtained from Sigma Chemical Company, in water (100 ml)/ethanol (300 ml). After 72 hours of rapid stirring, the solvent was removed in vacuo. Chromatography (Waters Prep 500, silica gel) of the residue with 15% methanol/methylene chloride gave 3.57 g (52%) of solid which had a melting point of 130°; $[\alpha]_D^{25}$ (1% CH_3OH) - 3.6°.

EXAMPLE 2

μ-1,2-BIS(DIPHENYLPHOSPHINO)ETHANE]BIS[(1-THIO-β-D-GALACTOPYRANOSATO-S)GOLD(I)]

Under an argon atmosphere at ambient temperature, a mixture of sodium thiogalactose (1.25 g, 5.4 mmol), obtained from Sigma Chemical Company, and μ-[1,2-bis-(diphenylphosphino)ethane]bis[chlorogold(I)] (2.34 g, 2.72 mmol), prepared as described in Example 1, in ethanol (150 ml)/water (20 ml)/chloroform (200 ml) was stirred for 18 hours. The solvent was removed in vacuo, and the residue subjected to preparative high pressure liquid chromatography (HPLC) (Waters Prep 500, silica gel, 20% methanol/methylene chloride) to give 0.64 g of oily product. Treatment with acetone followed by

recrystallization from methanol/ether gave 0.4 g (13%) of amorphous solid product; $[\alpha]_D^{25}$ (1% methanol) +3.9°.

EXAMPLE 3

μ-[1,2-BIS(DIPHENYLPHOSPHINO)ETHANE]BIS[(2,3,4,6-TETRA-O-ACETYL-1-THIO-α-D-MANNOPYRANOSATO-S)GOLD(I)]

Under an argon atmosphere at 0°, potassium carbonate (0.42 g, 3.1 mmol) in water (10 ml) was added to a solution 2-S(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-2-thiopseudourea hydrobromide (1.35 g, 2.77 mmol), prepared by the method of Durette et al., Carb. Res., 81, 261 (1980), in water (15 ml). After 15 minutes, ethanol (75 ml) was added and stirred 10 minutes followed by the addition of μ-[1,2-bis(diphenylphosphino)ethane]bis-[chlorogold(I)] (1.08 g, 1.25 mmol), prepared as described in Example 1, in chloroform (100 ml). After stirring overnight, water (150 ml) was added, the layers separated, the organic layer dried ($MgSO_4$), filtered and the chloroform removed in vacuo. Recrystallization of the residue from ethanol gave 0.87 g (46%) of white amorphorus solid; $[\alpha]_D^{25}$ (1% CH_3OH) + 52.1°.

EXAMPLE 4

μ-[1,2-BIS(DIPHENYLPHOSPHINO)ETHANE]BIS[1,THIO-α-D-MANNOPYRANOSATO-S)GOLD(I)]

A mixture of μ-[1,2-bis(diphenylphosphino)ethane]-bis[2,3,4,6-tetra-O-acetyl-1-thio- -D-mannopyranosato-S)-gold] (1.0 g, 2.1 mmol), prepared as described in Example 3, and concentrated ammonium hydroxide solution (15 ml) in methanol (100 ml) was stirred at ambient temperature for 18 hours and the solvent evaporated in vacuo. Water and methanol were added and the mixture acidified to pH 4 with glacial acetic acid. The solvent was evaporated in vacuo and the residue washed with water. Chromatography of the residue (silica gel, 30% methanol/methylene chloride) gave

an oily product which formed a white solid on treatment with acetone, and yielded 0.38 g (49%) of solid amorphous product; $[\alpha]_D^{25}$ (1% CH_3OH) + 52.2°.

EXAMPLE 5

μ-[1,2-BIS(DIPHENYLPHOSPHINO)ETHANE]BIS[2,3,4,6-TETRA-O-ACETYL-1-THIO-ß-D-GLUCOPYRANOSATO-S)GOLD(I)]

Under an argon atmosphere at ambient temperature, μ-[1,2-bis(diphenylphosphino)ethane]-bis[chlorogold(I)] (1.0 g, 1.16 mmol), prepared as described in Example 1, in chloroform (100 ml) was added dropwise to a solution of potassium carbonate (0.32 g, 2.32 mmol) and 1-ß-D-thio-2,3,4,6-tetra-O-acetyl-glucopyranose (0.84 g, 2.32 mmol), obtained from Aldrich Chemical Company, in water (40 ml)/ethanol (150 ml) followed by additional chloroform (50 ml)/ethanol (50 ml). After stirring for one hour, the solvent was evaporated *in vacuo* and the residue dissolved in chloroform, washed with water (twice), the organic layer dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Chromatography (Waters Prep 500, silica gel) of the residue with 20% ethyl acetate chloroform gave 1.6 g (91%) of product as a white amorphous solid; $[\alpha]_D^{25}$ (1% CH_3OH) -67.6°.

EXAMPLE 6

μ-[1,3-BIS(DIPHENYLPHOSPHINO)PROPANE]BIS[1-THIO-ß-D-GLUCOPYRANOSATO-S)GOLD(I)]

Under an argon atmosphere at ambient temperature, a suspension of μ-[1,3-bis(diphenylphosphino)propane]bis-[chlorogold(I)] (0.55 g, 0.64 mmol), prepared as described in Example 1, in chloroform (75 ml) was added to a rapidly stirred solution of sodium thioglucose (0.3 g, 1.4 mmol), obtained from Sigma Chemical Company, in methanol (75 ml)/water (10 ml). After one hour, the solvent was

removed in vacuo and the residue washed with water and decanted, methanol was added, the precipitate (NaCl) was collected from the ether/methanol solution, and ether added to the solution. After standing overnight the product was collected from the ether/methanol solution, washed with ether and dried to give 0.68 g (90%) of white solid which had a melting point of 125°.

EXAMPLE 7

μ-[1,2-BIS(DIPHENYLPHOSPHINO)ETHANE]-BIS[1-SELENO-β-D-GLUCOPYRANOSATO-SE)GOLD(I)]

a. μ-[1,2-Bis(diphenylphosphino)ethane]-bis[2,3,4,6-tetra-O-acetyl-1-seleno-β-D-glucopyranosato-se)gold(I)]

A solution of 0.69 g (5.0 mmol) of potassium carbonate in 3 ml of distilled water was stirred into an ice-cooled solution of 2.78 g (5.2 mmol) of 2-S (2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl(2-selenoisourea hydrobromide, prepared by the method of Wagner et al., Archiv. der Pharmazie, 297, 461 (1964), in 100 ml of water/methanol (1:1). The resulting suspension was stirred with 2.16 g (2.5 mmol) of μ-[1,2-bis(diphenylphosphino) ethane]bis[chlorogold(I)], prepared as described in Example 1, in 150 ml of chloroform. After one hour the chloroform layer was separated, concentrated in vacuo and the residue flash chromatographed on silica ($EtOAc/CHCl_3$ 1:1) to give 1.4 g of a white amorphous solid which had a melting point of 110-118°.

b. μ-[1,2-Bis(diphenylphosphino)ethane-bis[1-seleno-β-D-glucopyranosato-Se)gold(I)]

A mixture of 710 mg (0.44 mmol) of μ-[1,2-bis-(diphenylphosphino)ethane]bis[2,3,4,6-tetra-O-acetyl-1-seleno-β-D-glucopyranosato-Se)gold(I)], prepared as described in part a, and 50 mg (0.92 mmol) of sodium methoxide in absolute methanol was stirred at room

temperature until exchange of carbohydrate acetate with solvent was complete. Afterwards the mixture was cooled as excess sodium methoxide was neutralized by the addition of 0.053 ml of glacial acetic acid. The colorless solution was concentrated under reduced pressure. The solid residue was washed repeatedly with distilled water, collected and dried in vacuo to give 390 mg of pale yellow material which had a melting point of 130-135°.

EXAMPLE 8

μ-[1,2-BIS(DIPHENYLPHOSPHINO)ETHANE]-BIS[(2,3,5-TRI-O-ACETYL)(1-THIO-D-RIBOFURANOSATO-S)GOLD (I)]

a. 2,3,5-Tri-O-acetyl-D-ribofuranosylisothiouronium Bromide

Trimethylsilyl bromide, 4.9 g (0.032 mmol), was added dropwise to a stirred solution (0-5°) containing 5.0 g (0.016 mol) of ß-D-ribofuranose tetraacetate (Aldrich Chemical Company) in 30 ml of dry CH_2Cl_2 under argon. After the addition was completed, the mixture was allowed to warm and was maintained at room temperature (24 hrs) until conversion of the tetraacetate to triacetyl ribofuranosyl bromide was complete as indicated by ^1H NMR [J. W. Gillard, Tet. Letters, 22, 513 (1981)]. Thereafter, the reaction mixture was concentrated under reduced pressure to a thick oil, and the oil was reconcentrated twice after redissolution in CH_2Cl_2 to remove residual trimethylsilyl bromide. The residue was finally redissolved in 30 ml of acetone, treated with 1.22g (0.016 mol) of thiourea, and stirred at reflux temperature for 1/2 hr. Then the mixture was cooled, and the solid was removed by filtration. Then the solid was washed with cold acetone and dried in vacuo to give 2.7 g of product which had a melting point of 128-130°. The product was a mixture of α,ß-anomers as indicated by ^1H NMR (Gillard, cited above).

b. μ-[1,2-Bis(diphenylphosphino)ethane]-bis [(2,3,5-tri-O-acetyl)(1-thio-D-ribofuranosato-S)gold(I)]

A solution of 0.76 g (5.5 mmol) of potassium carbonate in 3 ml of distilled water was stirred into a cooled solution containing 2.16 g (5.2 mmol) of 2,3,5-tri-O-acetyl-D-ribofuranosylisothiouronium bromide, prepared as described above, in 100 ml of H_2O/MeOH (1:1). After the mixture had stirred in the cold for 1/2 hr, 2.16 g (2.5 mmol)) of μ-[1,2-bis(diphenylphosphino)ethane]-bis [chlorogold(I)], prepared as described in Example 1, dissolved in 150 ml of $CHCl_3$, was rapidly added dropwise. The mixture was then stirred an additional 2-1/2 hrs, and the $CHCl_3$ layer was separated and concentrated under reduced pressure to a thick syrup. The syrup was fractionated on silica gel (Baker Flash-Chrom) (25% MeOH/EtoAc) to give 1.97 g of product which was a mixture of α,β-anomers with the α-anomer predominating as indicated by ^1H NMR [J. W. Gillard, Tet. Letters, 22, 513 (1981)].

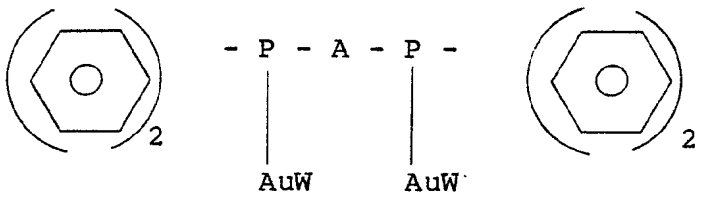
EXAMPLE 9

μ-[1,2-BIS(DIPHENYLPHOSPHINO)ETHANE]-BIS [1-THIO-D-RIBOFURANOSATO-S)GOLD(I)]

A mixture of 1 g (0.74 mmol) of μ-[1, 2-bis-(diphenylphosphino)-ethane]-bis[(2,3,5-tri-O-acetyl) (1-thio-α,β-D-ribofuranosato-S)gold(I)], prepared as described in Example 8, and 40 mg (0.74 mmol) of NaOMe in 50 ml of absolute MeOH was stirred under dry argon at room temperature for twenty minutes. It was then stirred with ion exchange resin (Biorad AG 50WX8, sulfonic acid form) until free of excess NaOMe. The resin was removed by filtration, and the filtrate was concentrated in vacuo. The oily residue was solidified by stirring water to give 480 mg of a white powder which had a melting point of 122-128°.

Claims for the Contracting States: BE, CH, DE, FR, GB, IT, LI, LU, NL and SE.

1. A [bis(diphenylphosphino)alkyl]bis-gold[I] compound of the formula



wherein:

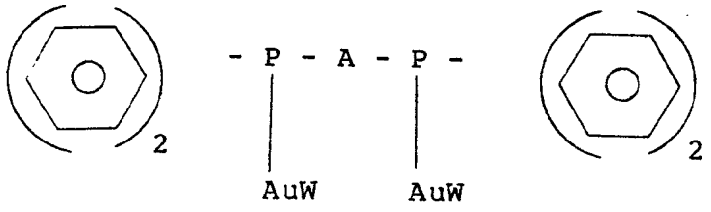
A is $(CH_2)_n$ or cis CH=CH;
n is 1 to 6; and
W is the same and is thiosugar or selenosugar.

2. The compound of Claim 1 wherein W is 1-thioglucose, 1-thiogalactose, 1-thiomannose, 1-thioribose, 1-thiomaltose, 1-thiofucose, 1-thioribofuranose, tetra-O-acetyl-1-thioglucose, tetra-O-acetyl-1-thiomannose, tetra-O-acetyl-1-thiogalactose, tri-O-acetyl-1-thioribose, hepta-O-acetyl-1-thiomaltose, tri-O-acetyl-1-thiofucose, 1-selenoglucose, 1-selenomannose, 1-selenogalactose, 1-selenoribose, 1-selenomaltose, or 1-selenofucose.

3. The compound of Claim 2 wherein W is 1-thioglucose, 1-thiogalactose or 1-thiomannose.

4. The compound of Claim 3 wherein A is $(CH_2)_2$ and W is 1-thioglucose.

5. A pharmaceutical composition which comprises a compound of the formula:



wherein:

A is $(CH_2)_n$ or cis CH=CH;
n is 1 to 6; and
W is the same and is thiosugar or selenosugar, and a pharmaceutically acceptable carrier.

6. The composition of Claim 5 wherein W is 1-thioglucose and A is $(CH_2)_2$.

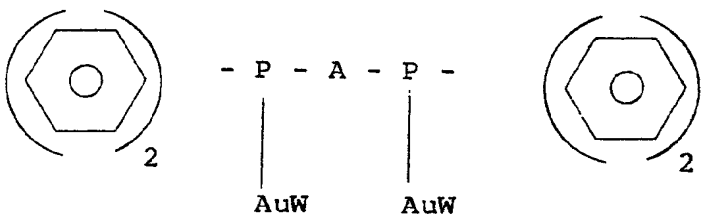
7. The composition of Claim 5 wherein the composition is in dosage unit form adapted for parenteral administration.

8. The composition of Claim 7 wherein the parenteral dosage unit is adapted to administer from about 5 to about 20 mg/m^2 of body surface.

9. A compound as claimed in Claim 1 for use as a therapeutic agent.

10. A compound as claimed in Claim 1 for use as a tumor growth-inhibiting agent.

11. A method for preparing a compound of formula (I):



(I)

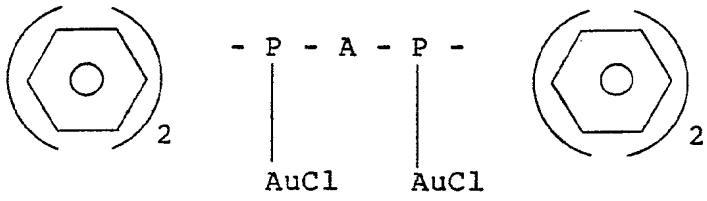
wherein:

A is $(CH_2)_n$ or cis CH=CH;

n is 1 to 6; and

W is the same and is thiosugar or selenosugar,

which comprises reacting the appropriate derivative of formula (II)



(II)

wherein A and W are as defined above, with

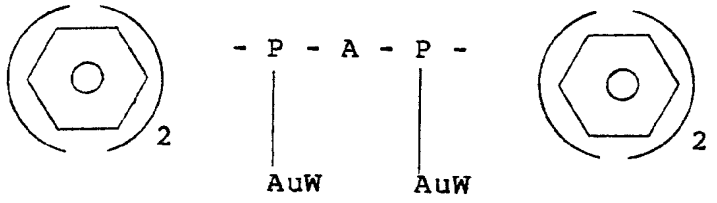
1) the appropriate sodium thiosugar or sodium selenosugar to prepare a compound of formula (I) wherein W is non-acetylated thiosugar or selenosugar; or

2) the appropriate per-O-acetyl-(thiopseudourea hydrobromide) to prepare a compound of formula (I) wherein W is acetylated thiosugar; or

3) the appropriate per-O-acetyl-(thiopseudourea hydrobromide) or per-O-acetyl-(selenopseudourea hydrobromide) to prepare an acetylated derivative of a compound of formula (I) wherein W is acetylated thiosugar or acetylated selenosugar, and treating the acetylated reaction product with a hydrolyzing base, to prepare a compound of formula (I) wherein W is non-acetylated thiosugar or selenosugar.

Claims for the Contracting State : AT.

1. A process for preparing a [bis(diphenylphosphino)alkyl]bis-gold[I] compound of the formula



(I)

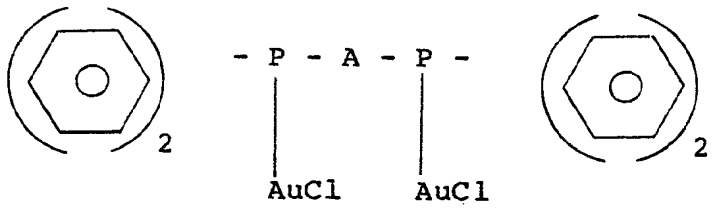
wherein:

A is $(CH_2)_n$ or cis CH=CH;

n is 1 to 6; and

W is the same and is thiosugar or selenosugar;

which comprises reacting the appropriate derivative of formula (II)



(II)

wherein A and W are as defined above, with

1) the appropriate sodium thiosugar or sodium selenosugar to prepare a compound of formula (I) wherein W is non-acetylated thiosugar or selenosugar; or

2) the appropriate per-O-acetyl-(thiopseudourea hydrobromide) to prepare a compound of formula (I) wherein W is acetylated thiosugar; or

3) the appropriate per-O-acetyl-(thiopseudourea hydrobromide) or per-O-acetyl-(selenopseudourea

hydrobromide) to prepare an acetylated derivative of a compound of formula (I) wherein W is acetylated thiosugar or acetylated selenosugar, and treating the acetylated reaction product with a hydrolyzing base, to prepare a compound of formula (I) wherein W is non-acetylated thiosugar or selenosugar.

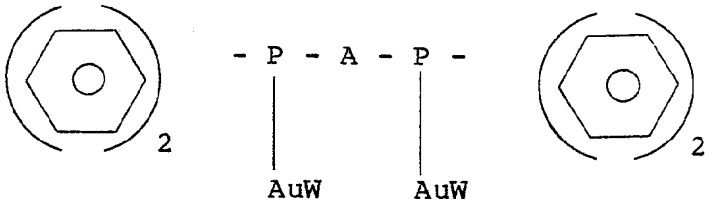
2. A process as claimed in Claim 1 in which the hydrolysing base is methanolic ammonia or sodium methoxide in methanol.

3. The process of Claim 1 or Claim 2 wherein W is 1-thioglucose, 1-thiogalactose, 1-thiomannose, 1-thioribose, 1-thiomaltose, 1-thiofucose, 1-thioribofuranose, tetra-O-actyl-1-thioglucose, tetra-O-acetyl-1-thiomannose, tetra-O-acetyl-1-thiogalactose, tri-O-actyl-1-thioribose, hepta-O-acetyl-1-thiomaltose, tri-O-acetyl-1-thiofucose, 1-selenoglucose, 1-selenomannose, 1-selenogalactose, 1-selenoribose, 1-selenomaltose, or 1-selenofucose.

4. The process of any one of Claims 1 to 3 wherein W is 1-thioglucose, 1-thiogalactose or 1-thiomannose.

5. The process of Claim 4 wherein A is $(CH_2)_2$ and W is 1-thioglucose.

6. A process for preparing a pharmaceutical composition which comprises admixing a compound of the formula:



wherein:

A is $(CH_2)_n$ or cis CH=CH;

n is 1 to 6; and

W is the same and is thiosugar or selenosugar, and a pharmaceutically acceptable carrier.

7. The method of Claim 6 wherein W is 1-thioglucose, 1-thiogalactose, 1-thiomannose, 1-thioribose, 1-thiomaltose, 1-thiofucose, 1-thioribofuranose, tetra-O-actyl-1-thioglucose, tetra-O-acetyl-1-thiomannose, tetra-O-acetyl-1-thiogalactose, tri-O-actyl-1-thioribose, hepta-O-acetyl-1-thiomaltose, tri-O-acetyl-1-thiofucose, 1-selenoglucose, 1-selenomannose, 1-selenogalactose, 1-selenoribose, 1-selenomaltose, or 1-selenofucose.

8. The method of Claim 7 wherein W is 1-thioglucose, 1-thiogalactose or 1-thiomannose.

9. The method of Claim 8 wherein W is 1-thioglucose and A is $(CH_2)_2$.

10. The method of Claim 6 wherein the composition is in dosage unit form adapted for parenteral administration.

11. The method of Claim 10 wherein the parenteral dosage unit is adapted to administer from about 5 to about 20 mg/m^2 of body surface.